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REMARKS

Claims 26-35 are pending and claims 26 and 35 have been amended. No new matter has been added.

Applicants acknowledge with appreciation that the Examiner has withdrawn the previous rejection of claims 26-35 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that "Claims 26-35 are still being examined as they read on the formula of the elected Group I compounds for treating cancer. Applicants are required to limit the instant claims to the formula of the elected Group I compounds."

In response, Applicants had previously canceled Claims 1-8 and 24 as drawn to a non-elected invention. However, the Examiner's requirement that Applicants reduce the scope of the instant claims defining "organic non-peptide compounds" to the elected Group I compounds is respectfully traversed.

Applicants' invention, as recited in Claims 26-35, is drawn to a *method* of treating a human patient for cancer by administering to said patient an effective amount of an organic non-peptide compound that binds, in said cells, to one or more domains of one or more of the patient's proteins of the p53 family, and stabilizes a functional conformation of the protein, thereby permitting the stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of the p53 protein. Claim 26 is a *generic* claim drawn to this invention. Claims 27-35 are method claims which depend from Claim 26. Claim 26-35 are not species claims that are drawn to a specific group of compounds.

Applicants respectfully submit that the Patent and Trademark Office ("PTO") has no statutory authority, nor any judicially created authority, to require Applicants to limit the scope of a generic claim, (i.e., claim 26) to a subgeneric concept defined by an Examiner (i.e., a method of treating cancer by administering Group I compounds), and impose it upon Applicants. Nor does the PTO have any authority to restrict Applicants' claims as reading upon an arbitrarily defined concept. It is Applicants' right under 35 U.S.C. § 112 to set the metes and bounds of their invention as they see it. *In re Wolfram*, 179 USPQ 620, 622 (CCPA 1973).

The Office Action, by requiring Applicants to limit the scope of their claims to

Group I compounds, has inappropriately dissected Applicants' independent claim (claim 26) into multiple parts such that Applicants are now deprived of their statutory rights under 35 U.S.C. § 112 to "claims particularly pointing out and distinctly claiming the subject matter which *Applicant regards as his invention.*" The Examiner has, in effect, carved out a portion of Applicants' invention. This the PTO can not do. The courts have consistently ruled that any attempt by the PTO to reject a *single* claim (here, claim 26) as embracing more than one invention under 35 U.S.C. § 121 violates the basic right of an applicant to claim his invention as he chooses. *In re Weber*, 198 USPQ 328, 331-32 (CCPA 1978); *In re Haas*, 198 USPQ 334, 336 (CCPA 1978); *see also In re Watkinson*, 14 USPQ2d 1407, 1409 (Fed. Cir. 1990).

Applicants wonder if the Examiner intended to request election of a species for initial examination, which would be followed, if a determination of patentability is reached by examination of the remainder of the claim's scope. Clarification is respectfully requested.

STATUS OF THE CLAIMS

Following entry of this amendment, claims 26-35 will be pending. Claims 26 and 35 have been amended.

Support for the amended claims is as follows:

Claim 26: page 12: lines, 20-29, 31-35; and, page 13: lines 1-2, 12-15.

Claim 35: page 12: lines, 20-29, 31-35; and, page 13: lines 1-2, 12-15.

Rejection Under §103(a)

Claims 26-35 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Carter et al. reference taken with the Kaneko et al. reference, hereinafter the "Carter/Kaneko" references.

The Carter et al. reference teaches that the anticancer agents etoposide and nitomycin are effective in treating certain cancers. The Kaneko et al. reference teaches that the "anticancer drugs etoposide and nitomycin C increased nuclear p53 protein... ."

Applicants submit that the Carter reference taken with the Kaneko et al. reference does not render claims 26-35 obvious. Applicants respectfully submit that "Carter/Kaneko" references do not teach or suggest Applicant's invention. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so in either the references themselves or in the knowledge generally available to one of ordinary skill in the

art, *In re Jones*, 21 USPQ2nd 1941 (Fed. Cir. 1992). The Examiner has not pointed to any teaching or suggestion in the "Carter/Kaneko" references of compounds used to stabilize functional conformation of p53 or of compounds used to increase the activity of p53 as presently claimed. Further, the "Carter/Kaneko" references provide no teaching or suggestion of using compounds to bind to one or more domains of a human protein of the p53 family under physiological conditions permitting the p53 protein to interact with one or more macromolecules that participate in a wild-type activity of the p53 protein. Furthermore, there is no teaching in these references of using compounds that bind to one or more domains of a mutant p53 protein under physiological conditions permitting the stabilized mutant p53 protein to interact with one or more macromolecules that participate in wild-type activity. In contrast, the Kaneko reference teaches that the use of compounds etoposide and mitomycin C results in a quantitative response because use of etoposide and mitomycin C results in an increase in the **amount** of non-mutant p53 protein and a decrease in the **amount** of proliferating cell nuclear antigen. Further, the Kaneko reference teaches that when compounds are present that suppress an increase in the amount of p53 protein, the resulting level of inadequate DNA repair is due to the reduced **accumulation** of p53 protein. Applicants respectfully submit that the Kaneko references does not teach or suggest that the anti-cancer compounds of the present invention can be used to stabilize functional conformation of wild-type and mutant p53 resulting in normal or increased wild-type activity as presently claimed.

In view of the comments above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 26-35 under 35 U.S.C. 103(a) as obvious over the "Carter/Kaneko" references.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 26-35 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the specific cancers disclosed, does not reasonably provide enablement for the term "cancer." Specifically, the Examiner states that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The term "cancer" in claims 26-35 lacks clear exemplary support in the specification as filed."

Applicants wish to address the Examiner's objection to the term "cancer." The present invention is drawn to a method of treating a human patient for cancer that can be treated by increasing the activity of one or more proteins of the p53 family in cells affected by said cancer, comprising the steps of administering to said patient an effective amount of an organic non-peptide compound that binds, in said cells, to one or more of the domains of the patient's proteins of the p53 family, and stabilizes a functional conformation of said proteins under physiological conditions, and permitting said stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of said protein. (See, e.g., the specification at p. 13). The specification provides ample guidance to one having ordinary skill in the art to practice the claimed method of treating cancer without undue experimentation.

It is well known that many cancers are associated with conformational defects in the proteins of the p53 family, caused by, e.g., mutations in the p53 family genes. As the specification at p. 1 states, "mutants of p53 are the most common genetic aberration in cancer." This is clearly demonstrated by the following illustrative quotes from many highly respected journals:

> "The p53 guardian of the genome is inactivated in the majority of cancers, mostly through missense mutations that cause single residue changes in the DNA binding core domain of the protein." A. Signal, et al., Cancer Research 60, 6788-6793 (Dec. 15, 2000).
>
> "Perturbation of p53 protein function is a common, if not universal, finding in human cancer." W. Kaelin, Jr., Journal of the National Cancer Institute, Vol. 91, No. 7 (April 7, 1999).
>
> "TP53 is the most frequently mutated gene in human cancers and is thought to play a crucial role in malignant transformation." A. Zeimet, et al., Biochemical Pharmacology, Vol. 60, pp. 1153-1163 (2000).
>
> "Given that human cancers are biologically and pathologically quite distinct, it has been quite surprising that a common event, perturbation of the p53 pathway, occurs in most if not all types of human cancers." T. Hupp, et al., Biochem. J. 352, 1-17 (2000).
>
> "One protein -- p53 -- plays nemesis to most cancers by condemning damaged cells to death or quarantining them for repair." A. Bullock, et al., Nature Reviews, vol. 1, pp. 68-76 (2001).

> "[T]he majority of human cancers overall carry mutant p53 genes." M. Smith, et al., Cancer Biology & Therapy, Internet pre-published on Sept. 5, 2001 as Manuscript MS# 08-30-02.
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> "The p53 gene is lost or mutated in most human cancers." The Journal of Antibiotics, vol. 54, no. 10 (Oct. 2001).
>
> "Mutation of p53, which is the most frequent genetic alteration detected in human cancers, inactivates these growth regulatory functions and causes a loss of tumor suppressor activity." C. Cadwell, et al., Gene 277 15-30 (2001).
>
> "p53, perhaps the single most important human tumor suppressor, is commonly mutated in human cancers." A. Grimberg, Molecular Genetics and Metabolism 70, 85-98 (2000).
>
> "Mutations in the p53 tumor suppressor are the most frequently observed genetic alterations in human cancer." Y. Cho, et al., Science, 265, pp. 346-355 (1994).

The present specification teaches a method of treating cancer by administering an effective amount of an organic non-peptide compound that is capable of binding to one or more domains of a human protein of the p53 family under physiological conditions, and thereby stabilizing a functional conformation of the protein, permitting the stabilized protein to interact with one more macromolecules that participate in a wild-type activity of the protein. As the specification makes clear, the specific cancers listed in the disclosure (see p. 34-35) are merely examples of cancers associated with mutations in the p53 proteins. The specification at p. 35 expressly states that "[t]he above cancers, and others, are treatable by the methods and compounds of the invention." (Emphasis added.) The Examiner has offered no evidence that undue experimentation is required for one skilled in the art to practice the claimed method, especially in view of the broad role played by p53-type proteins in cancer.

Moreover, the PTO has consistently issued patents with claims to methods of treating "cancer" with limited support in the specification. The present specification provides very detailed support in the specification, and indeed provides first ever disclosure of a basic biological mechanism, that small non-peptide organic compounds can stabilize proteins of the p53 family to great benefit including in an ex-vivo xenograft model.

The following 25 patents are illustrative of circumstances where the U.S. Patent Office issued claims to the treatment of CANCER. It is submitted that the Examiner has misapplied the law, and that the present Applicants are entitled to equal consideration under that law.

Patents	Claims to Treating Cancer	Support in Specification
6,395,771	3, 4, 11, 12	Leukemia cells, and ovarian, breast, lung, and cervical cancers. (Col. 9, 11. 30-60.)
6,403,554	25-30	General statement of cancer treatment with no examples. (Col. 2, 11. 5-10.)
6,399,638	6, 7	Laundry list of cancers and tumors (col. 5, 11. 60-67; col. 6, 11. 1-19.), with only one example of a cytotoxicity assay using coloncarcinoma cells. (Col. 36, ll. 49.)
6,399,653	13	General statement of treatment of cancer with no examples. (Col. 2, ll. 54-61.)
6,399,647	1	Human colon cancer. (Col. 34, ll. 11-49.)
6,399,583	10	Uterine sarcoma cells, Lewis lung carcinoma cells, melanoma cells, lung squamous cell carcinoma, leyding cell tumor, mouse lymphocytic leukemia cells, and P388 leukemia. (Cols. 20-22.)
6,399,598	20, 22	Premetastatic tumor. (Col. 42, ll. 43-65.)
6,403,625	6	Stomach cancer, esophageal carcinoma, duodenal carcinoma, rectum cancer with

		no examples. (Col. 5, ll. 47-51; col. 6, ll. 44-47.)
6,403,569	1	Colorectal cancer. (Col. 1, ll. 7-15; col. 6, ll. 7-13)
6,403,592	10	Small cell lung carcinoma with no examples. (Col. 11, ll. 59-60.)
6,406,699	1	Breast cancer, astrocytoma, renal cell carcinoma. (Cols. 11, 18, 20.)
6,395,749	20	General statement of cancer treatment with examples of human prostate cancer and an unspecified tumor. (Col. 13, ll. 61-62; col. 15, ll. 40-43; Exs. 12 and 13.)
6,384,049	1, 12	Laundry list of cancers with only one example of colon cancer tumor in mouse. (Cols. 3-5; Ex. 1.)
6,392,063	43, 44	Cancer of the brain, stomach, lung, colon, prostate, breast, ovary, head or neck, and leukemia, lymphoma, carcinoma, or sarcoma. (Col. 5, ll. 10-13.)
6,387,903	4, 5	Human pancreatic carcinoma. (Exs. 20-22.)
6,391,888	2	General statement of treating cancer, such as solid tumors and leukemia. (Col. 6, ll. 38-44.)
6,372,785	5, 8	Carcinomas, sarcomas, melanomas, and lymphomas affecting organs such as lungs, mammary tissue, prostate gland, intestines, liver, heart, skin, pancreas, and brain. (Col. 5, ll. 55-67.)

6,388,131	21	General statement of treating cancer with examples of human cervical carcinoma. (Col. 10, ll. 61-65; Ex. 28.)
6,391,302	1	General statement of treating cancer. (Col. 3, ll. 55-57; Ex. 2.)
6,391,913	11	General statement of cancer treatment. (Col. 2, 11. 66-67.)
6,387,673	1	General statement of cancer treatment with no examples. (Col. 6, 11. 40-45.)
6,391,853	47	General statement of cancer treatment with no examples. (Col. 2, 11. 55-64; col. 3, ll. 7-9.)
6,391,916	24, 30	General statement of treating cancer with examples of mice T leukemia cells. (Col. 3, 11. 37-40; Ex. 69.)
6,395,729	7, 13	General statement of treating cancers and tumors with no examples. (Col. 7, 11. 42-67; col. 8, 11. 1-5.)
6,359,000	1	General statement of treating cancer with no examples. (Col. 1, 11. 11-14; col. 2, 11. 44-50.)

Accordingly, Applicants respectfully submit that it is improper for the Examiner to require the claims to be limited to the specific cancers listed in the specification. In view of the above arguments, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. § 112, first paragraph is improper and respectfully request that the rejection of claims 26-35 under 35 U.S.C. §112, first paragraph be withdrawn.

Applicants note that the Examiner in his January 17, 2003 communication, stated that "changing the term 'cancer' to 'a cancer disease state is associated with possession of a mutant protein of the p53 family' would overcome this rejection." Therefore, to expedite prosecution of this case, Applicants herein submit amended Claim 26 incorporating the

Examiner's suggestion to recite "[a] method of treating a human patient for a cancer disease state normally associated with possession of a mutant protein of the p53 family that can be treated by increasing the activity of one or more proteins of the p53 family in cells affected by said cancer disease state, comprising the steps of: (a) administering to said patient an effective amount of an organic non-peptide compound that binds, in said cells, to one or more domains of one or more of the patient's proteins of the p53 family, and stabilizes a functional conformation of said proteins under physiological conditions, and (b) permitting said stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of said protein."

Applicants respectfully submit that this amendment obviates the Examiner's rejection under 35 U.S.C. § 112, first paragraph and respectfully request that the rejection of claims 26-35 under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

For the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejection set forth in the August 21, 2003 Office Action. In view of the foregoing amendment and remarks, Applicants respectfully submit that the instant application is now in condition for allowance. Issuance of a notice to that effect is respectfully solicited.

If the Examiner wishes to comment or discuss any aspect of this application or response, Applicants' undersigned attorney invites the Examiner to call her at the telephone number provided below.

Respectfully submitted,

Date: November 19, 2003

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